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Are stroke survivors with delirium at higher risk of post-stroke dementia? Current evidence and future directions

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Objectives: The idea that delirium is a risk factor for dementia, broadly defined, is derived from heterogeneous patient samples. We reviewed available evidence as to whether stroke survivors who developed delirium during the acute phase of treatment are at a higher prospective risk of incident post-stroke cognitive impairment or dementia.

Design: We searched 8721 records in the Cochrane database for reviews or protocols dealing with the study objective, Medline, EMBASE, PsycInfo and CINAHL for observational studies in the general adult population and PubMed for in-process articles. Additional searches of the reference lists of retrieved articles were also undertaken. Qualitative syntheses and meta-analysis were conducted according to conventional guidelines.

Results: Twelve relevant articles were fully appraised. Four out of these studies, comprising 743 stroke survivors, including 199 with delirium, met criteria for qualitative syntheses. Overall, the studies presented low to moderate level evidence suggesting an association between post-stroke delirium and dementia.

Conclusions: There is a need for further studies to investigate the association of post-stroke delirium and dementia using well-defined cohorts of patients and controlling for factors such as pre-stroke cognition, stroke severity and location and the presence of persistent delirium. Such studies will help understand the place of delirium identification and prevention in reducing the risk of dementia after stroke.

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Key words: vascular dementia; prevention; risk factor; acute confusional state

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Background

Delirium is a transient neuro-behavioural syndrome that may reflect the impact of a general medical condition, or its treatment, on the brain (American Psychiatric Association, 2000). It is especially common among older persons admitted to in-patient care settings, where rates such as 14% (Inouye, 2006) and 20% (Royal College of Physicians, 2006) have been reported. Cerebrovascular accident or stroke is an important cause of delirium, found in up to 48% of survivors during the acute phase (Kokmen *et al.*, 1996; McManus *et al.*, 2007).

Regardless of the primary diagnosis leading to delirium, it is often suggested that delirium itself is an

index of several poor outcome criteria in hospital treated patients (Fick *et al.*, 2002; Inouye *et al.*, 2007; Pendlebury and Rothwell, 2009; Witlox *et al.*, 2010; Brainin *et al.*, 2015). In particular, there is compelling evidence to suggest long term cognitive impairment after the resolution of the underlying physical illness and other features of the delirium (Wacker *et al.*, 2006; Bickel *et al.*, 2008) with consensus that delirium is a risk factor for dementia, broadly defined (Royal college of Psychiatrists, 2005; Royal College of Physicians, 2006). However, it is unclear whether the association has been consistently demonstrated in the specific context of cognitive impairment following stroke, including vascular dementia. The present systematic review aims to investigate the strength of

evidence linking post-stroke delirium with post-stroke cognitive impairment and dementia.

Methods

This review followed conventional recommendations for the methodology and reporting of systematic reviews (Moher *et al.*, 2009; National Institute for health and Care Excellence, 2012). First, a scoping search of the Cochrane database was conducted for existing systematic reviews or protocols dealing with the review question. Next, a comprehensive literature search was conducted using MEDLINE (Ovid SP 1946 to 23 July 2015), EMBASE (Ovid SP 1974 to 24 July 2015), PsycINFO (Ovid SP 1806 to 7 October 2015) and CINAHL (EBSCO host, 7 October 2015) databases. For the searches, a facet analysis of the research question (National Institute for health and Care Excellence, 2012) was constructed (Population: post-stroke patients; exposure: delirium; comparison: no delirium; outcome: cognitive impairment). Variations of the component of each facet in the thesaurus and indexing terms in the MeSH (Medline and Cochrane library) were analysed. Alternative words, spellings, plurals and abbreviations of each item in the facets were also considered. The following keywords were used for the searches with the 'explode' operator: 'cerebrovascular accident', stroke, 'post stroke', delirium, 'acute confusional state', dementia, 'vascular dementia', 'Alzheimer's disease', 'cognitive impairment' and 'cognitive disorder'. A search of the PubMed database (1966 to 19 March 2015, repeated for updates on 7 October 2015) was also conducted to retrieve 'in-process' and 'ahead of print' citations. For this, the following key words were combined: stroke/'post stroke' and delirium/'acute confusional state' and dementia/cognition/'cognitive impairment'/'cognitive dysfunction'. The database searches were limited to English language and human literature. Additional limit was set for observational studies in the adult population (≥ 19 years). Limits on publication dates were not imposed. Additional hand searching of the reference list of relevant articles retrieved from the databases was also implemented.

Search results

The combined database and hand searches identified a total of 2749 records. Duplicates of the records in either database (795) were excluded. After screening of the titles and abstracts, a further 1942 materials were excluded leaving 12 articles of potential relevance

to the review question. After reading through the full text of these papers, a further eight articles (Gustafson *et al.*, 1991; de Rooij *et al.*, 2006; McManus *et al.*, 2009; Oldenbeuving *et al.*, 2011; Mitsova *et al.*, 2012; Hong *et al.*, 2013; Miu and Yeung, 2013; Cole *et al.*, 2014) were excluded as they did not specially address post-stroke dementia or cognitive impairment among several outcomes of post-stroke delirium. Details of number of included and excluded studies are shown on the PRISMA flow chart (Moher *et al.*, 2009) in Figure 1.

Critical appraisal of selected studies

Four studies (Henon *et al.*, 1999; Sheng *et al.*, 2006; van Rijsbergen *et al.*, 2011; Melkas *et al.*, 2012) with direct bearing on the review question were selected for appraisal. All included consecutive older adults admitted acutely for in-patient care after a stroke. The diagnosis of delirium was based on standard clinical criteria using the confusion assessment method (CAM) (Inouye *et al.*, 1990). This was achieved within 3 (Sheng *et al.*, 2006), 7 (van Rijsbergen *et al.*, 2011; Melkas *et al.*, 2012) or 12 days (Henon *et al.*, 1999) of admission. Together the studies pooled 743 acutely admitted older stroke survivors, of which 199 had

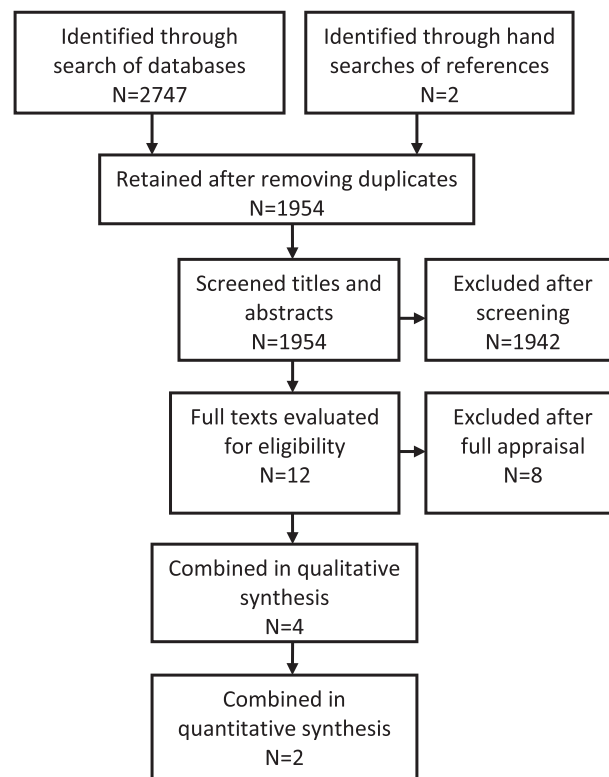


Figure 1 PRISMA flow chart for included and excluded studies.

delirium. In Melkas *et al.*, the diagnosis of dementia was made 3 months after the stroke using the 'clinician best judgement' in line with Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. In van Rijsbergen *et al.*, the diagnosis of dementia was made at 2 years after the stroke using the Clinical Dementia Rating scale (CDR) (Morris, 1993). In the remaining two studies, no specific diagnosis of dementia was made but cognitive functioning was measured using the mini-mental state examination (MMSE) (Folstein *et al.*, 1975) at 6 months in Henon *et al.*, and at 12 months post stroke in Sheng *et al.* Key information about the four included studies is summarised in Table 1.

Qualitative synthesis and summary of major findings

A standard framework for appraising prognostic studies was used to assess the quality of the selected studies (National Institute for health and Care Excellence, 2012). The studies clearly described the source population, sampling frame, baseline sample and the criteria for inclusion and exclusion. Appropriate statistical methods were used and potential confounders of the outcome of interest examined. Weaknesses of the studies included inadequate reporting or accounting for attrition. Cognitive outcome was based on the MMSE in Sheng *et al.* and Henon *et al.*, which may overestimate cognitive impairment after stroke through language deficits. Strengths of the studies included the demonstration of large effects for the outcome and a dose response relationship for the outcome in Sheng *et al.* Overall, the NICE grading criteria classed the evidence as low to moderate quality. Within this limitation, the studies were consistent in finding post-stroke delirium was associated with greater cognitive impairment or increased risk of dementia.

Meta-analysis of mini-mental state examination outcome in patients with and without post-stroke delirium

Differences in cognitive outcome measures coupled with non-reporting of complete outcome data meant that we could only combine two of the four studies in a meta-analysis based on MMSE score (Henon *et al.* and Sheng *et al.*). Using the Review Manager (RevMan) version 5.3 software (The Cochrane Collaboration, 2014) we carried out a fixed-effect analysis. Mean and standard deviations of MMSE scores were used to derive the study effect measure (mean difference in MMSE score). The inverse of variance method

was used for weighting. The forest plot in Figure 2 shows a reduction in MMSE in patients with delirium compared with those without. When pooled, the overall effect suggests an increase in post-stroke cognitive impairment with delirium (Mean MMSE reduction 4.8, 95% CI = 3.4–6.3).

Discussion and clinical implications

The current systematic review found very little evidence specifically addressing a link between post-stroke delirium and dementia, limiting the ability to draw firm conclusions as to whether such an association is present or not. However, an understanding of this association is of potential clinical importance as many of the known predictors of dementia after vascular pathology such as older age, male gender and the presence of co-morbid diseases (Roman *et al.*, 1993; Roman, 2004) cannot be modified. If post-stroke delirium is found to be a risk factor for post-stroke dementia, the dementia might be preventable or ameliorated using simple measures such as improved awareness and treatment of delirium through education (Tabet *et al.*, 2005; Inouye *et al.*, 2010) or avoidance of medications associated with delirium (Han *et al.*, 2001; Inouye, 2004; Inouye *et al.*, 2014). The presence of delirium after stroke might also help clinicians and policy advisors plan rehabilitation and long term care after stroke if cognitive outcome could reliably be predicted. Further studies are thus required to clarify the association between post-stroke delirium and post-stroke dementia. In reviewing the existing evidence, a number of theoretical and methodological issues have emerged that are of potential relevance for the design of such future studies.

Pre-stroke cognition

Three of the studies reviewed did not adequately measure or control for pre-stroke dementia (Sheng *et al.*, 2006; van Rijsbergen *et al.*, 2011; Melkas *et al.*, 2012). Pre-existing cognitive impairment or dementia may be an independent risk factor for delirium (Fong *et al.*, 2012, 2015), as the pathological brain may be less resilient to the onset of the syndrome. This is especially so in the presence of other vulnerabilities (Fong *et al.*, 2009, 2012, 2015). Furthermore, delirium may be evidence of an emerging or prodromal dementia (Jackson *et al.*, 2004; Fong *et al.*, 2015) and shares the same inflammatory processes, cytokine release, and changes in blood–brain barrier permeability that occur in dementia (Di Bona *et al.*, 2010). Given this

Table 1 Are stroke survivors with delirium at higher risk of post-stroke dementia?

Reference	Study type	Study quality	Number of patients	Patient characteristics	Risk factor	Follow-up	Outcome measure	Source of funding
Melkas <i>et al.</i> (2012)	Prospective cohort study	Moderate	263	Acutely admitted for ischaemic stroke aged 55–85 years	Delirium (DSM IV)	3 months	Dementia (DSM IV)	Helsinki University Central Hospital, Finland
Van Rijsbergen <i>et al.</i> (2011)	Nested case-control	Low to moderate	122	Acutely admitted ischaemic/haemorrhagic stroke, mean age of 75.2 ± 10.5 years	Delirium (CAM)	2 years	Dementia (CDR ≥ 1)	Non disclosed
Sheng <i>et al.</i> (2006)	Prospective cohort study	Low to moderate	156	Acutely admitted for ischaemic/haemorrhagic stroke aged ≥ 65 years	Delirium (DSM IV)	12 months	Cognitive functioning (MMSE)	Health Research Foundation, Sydney, Australia
Henon <i>et al.</i> (1999)	Prospective cohort study	Moderate	202	Acutely admitted Ischaemic/haemorrhagic stroke, median age of 75 (42–101) years	Acute confusional state (DSM IV)	6 months	Cognitive functioning (MMSE)	Ministry of Education, Research and Technology, France

DSM IV, Fourth revision of the Diagnostic and Statistical Manual of Mental Disorders; CAM, Confusion Assessment Method; CDR, Clinical Dementia Rating Scale.

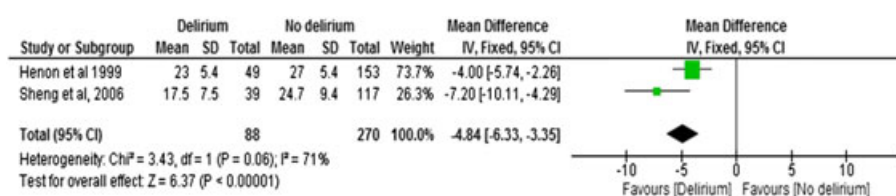


Figure 2 Forest plot showing reduction in MMSE at follow-up in patients with post-stroke delirium compared with those without.

possible bi-directional relationship between delirium and dementia (dementia as a risk for delirium and delirium as a risk for dementia), studies seeking to investigate the impact of delirium on dementia may generate robust, but inaccurate, estimates of association between the two conditions if they fail to control for pre-existing dementia.

Persistent delirium

In patients with prolonged delirium, the possibility of misdiagnosing delirium as dementia arises, the shorter the time between delirium onset and dementia diagnosis, the greater the possibility of misclassification. In one of the studies reviewed (Melkas *et al.*) dementia was diagnosed 3 months after stroke when ongoing effects of delirium might still have been present. In the three remaining studies, cognitive impairment was assessed at between 6 months and 2 years where ongoing delirium is less likely to have been an issue. Demonstration of the resolution of delirium at the point of diagnosis of dementia is thus an important consideration for future studies. This is particularly relevant in the context of vascular dementia given that NINDS–AIREN research diagnostic criteria (Roman *et al.*, 1993; Roman, 2004; Wiederkehr *et al.*, 2008a; Wiederkehr *et al.*, 2008b) specify ‘...onset of dementia in three months following a recognised stroke’. Many studies make the diagnosis of dementia at 3 months post-stroke without specifically excluding delirium, (for example, Pohjasvaara *et al.*, 1997; Klimkowicz *et al.*, 2002; Tang *et al.*, 2004; Zhou *et al.*, 2004) potentially overestimating the post-stroke outcome of vascular dementia.

Stroke severity, recurrence and location

The studies reviewed did not control for stroke severity, stroke lesion location and whether a first or recurrent stroke. It may be that a more severe stroke (Ojagbemi and Owolabi, 2013) or a second stroke increases the likelihood of delirium and has a greater impact on cognitive outcome. This would lead to a

‘noise’ association between delirium and dementia that need not imply delirium has caused the dementia. Similarly, particular brain locations, for example, the posterior cerebral artery territory or top of the basilar syndrome (Caplan, 1980; Lazzarino De Lorenzo *et al.*, 2014), may increase the likelihood of delirium and functional deficits associated with poorer outcome, without implying a causal link.

Diagnostic specificity

Post-stroke dementia is an umbrella term for all dementias occurring after a stroke and may include Alzheimer’s pathology, Lewy body dementia, and mixed dementia (Leys *et al.*, 2005). The studies reviewed do not specify whether post-stroke delirium influences the risk for all post-stroke dementias or is specific to a subtype, for example, vascular dementia. It is possible that post-stroke delirium increases the risk of some dementia subtypes but not others, and it would therefore be important to better specify the outcome dementia subtype in future studies.

In conclusion, the strength of current evidence for the impact of post-stroke delirium in potentiating the development of post-stroke dementia or cognitive impairment is low to moderate and lacks specificity. There remains a gap in the literature on whether an association is present or not and, if present, its wider clinical significance. Well-designed cohort studies will be important to answer this question and the role of delirium management in the secondary prevention of dementia after stroke.

Key points

- Post-stroke delirium has been little studied as a risk factor for post-stroke dementia with only four studies of low to moderate quality identified.
- Existing studies show significant variability in design and outcome measures.
- Future studies should consider controlling for pre-stroke cognition, stroke severity and location, persistent delirium and specify dementia subtype.

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